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SUPPLEMENT ARTICLE

Addressing challenges associated with long-term topical treatment and benefits of proactive management in patients with psoriasis

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Abstract The majority of patients with psoriasis vulgaris (chronic plaque psoriasis) can be treated successfully with short-term topical therapies. However, long-term management of psoriasis with topicals is challenging and tends to take a reactive approach to disease relapse, rather than a proactive approach aimed at maintaining disease remission. Patients are often dissatisfied with the delay in treatment response and inconvenience of applying topical treatments, and therefore frequently discontinue treatment leading to poor outcomes. Relapse is common, particularly with reactive management, as underlying residual disease can remain following initial skin clearance; some patients find that their disease at relapse may be worse than their initial symptoms. This can have a detrimental effect on patient quality of life (QoL) and increase the risk of psoriasis-associated depression. A long-term proactive management approach, with maintenance treatment following initial treatment success, could help sustain disease remission and improve clinical and QoL outcomes for patients. Treatment with fixed-dose calcipotriol 50 μg/g betamethasone dipropionate 0.5 mg/g cutaneous foam (Cal/BD foam) is effective in the short term, providing a fast onset of action and improvements in disease at 4 weeks. Results from the Phase III PSO-LONG study demonstrated that long-term proactive management was superior to reactive management in prolonging time to first relapse, reducing number of relapses and increasing days in remission in adults with psoriasis vulgaris. Furthermore, Cal/BD foam was well tolerated in PSO-LONG. No new safety concerns were identified over 52 weeks; the safety profile was consistent with that described previously. Given this, Cal/BD foam should be considered when prescribing topicals for the long-term proactive management for patients with psoriasis.
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Conflicts of interest

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Introduction

Several therapies are available for the treatment of psoriasis vulgaris (chronic plaque psoriasis) including topical agents (e.g. corticosteroids, vitamin D_3 analogues), phototherapy, conventional systemic therapies or biologics (e.g. methotrexate, etanercept, adalimumab).[1] Despite the availability of many treatment options, a substantial proportion of patients do not achieve complete and sustained disease resolution, and often experience reduced quality of life (QoL).[2,3] Long-term management of psoriasis is challenging, not only because of the recurrent, relapsing nature of the disease, but also the delay in treatment response and poor patient adherence to treatment that is frequently reported.[4,5] Declining response and non-adherence to therapy can lead to poor outcomes for patients.[4] Thus, a fast-acting treatment, which is patient friendly and can achieve long-term disease control, is needed to help improve patient outcomes.

The majority of patients with psoriasis can be treated solely with topical treatments.[4,6] Currently, long-term topical psoriasis treatment relies on a reactive approach to disease relapses, as opposed to continuous long-term proactive management aimed at maintaining disease remission.[7] Recently, a panel of experts recommended that long-term management should be considered essential to ensure patients receive appropriate proactive treatment, which may help to optimise adherence and improve long-term outcomes for patients.[5]

Fixed-dose combination calcipotriol 50 μg/g betamethasone dipropionate 0.5 mg/g (Cal/BD) cutaneous aerosol foam (Enstilar®; LEO Pharma, Ballerup, Denmark) is approved in the US (in adults and adolescents) and EU (in adults) for the treatment of psoriasis vulgaris for 4 weeks.[8,9] The Phase III PSO-LONG study (NCT02899962) assessed the efficacy and safety of long-term (52 weeks), twice-weekly proactive management with topical Cal/BD foam versus vehicle foam (reactive management with Cal/BD foam as rescue treatment) in the prevention of disease relapse in adults with psoriasis.[10] Here, we focus on providing a rationale for the potential benefits of proactive versus reactive treatment in the long-term management of psoriasis, using evidence from the PSO-LONG study.

Current approach and challenges to the long-term management of psoriasis with topical therapies

Numerous topical therapies, in varying strengths and vehicles of administration, are available for the treatment of psoriasis (Table 1).[11] They are applied to the affected areas of skin (plaques) in a variety of formulations, including ointments, creams, solutions, lotions, gels or foams. The choice of vehicle formulation is key in the successful treatment of psoriasis, as this can significantly alter the adherence and the penetration of a topical treatment, therefore reducing therapeutic efficacy and potency.[6,12] The type of product used is dependent on various factors, including the location of the plaque and the condition of the skin. Typically, topical corticosteroids are administered during acute episodes of psoriasis. Some patients may use topical treatments more frequently as part of a long-term treatment approach.[12,13] This long-term management is usually in response to disease 'flares' or relapses.[7]

Despite topical therapies being available for several decades, there are limited controlled studies and guidance on their long-term use in the management of psoriasis.[14] In addition to limited guidance, there are also safety concerns associated with long-term use of some topicals. For example, corticosteroids are highly efficacious and currently the cornerstone of topical psoriasis treatment; however, associated adverse effects, (e.g. atrophy, hypopigmentation) prohibit their use as a long-term management approach.[11] Many patients have a 'phobia' to using corticosteroids as a consequence of potential adverse effects, often leading to patient non-adherence to the treatment regimen.[5,15] Furthermore, there have also been reports of declining efficacy with long-term corticosteroid use.[16]

Patient non-adherence to therapy greatly affects the efficacy of long-term topical treatment. Factors influencing non-adherence include patient dissatisfaction with treatment efficacy, inconvenience of application and fear of side effects.[17,18] Although topical treatments are effective, they must be used according to the label and consistently for a period of weeks to months before clinical evidence of improvement can be seen, which can often create the perception that the treatment is not working.[4] This in turn contributes to patient dissatisfaction and non-adherence to the treatment regimen, leading to poor outcomes.[4,18]

Limited guidance on the approach to long-term therapy and addressing patient non-adherence, coupled with the fact that psoriasis is a chronic relapsing disease, contributes to the challenges of effective long-term management of psoriasis. Strategies to prolong or prevent remission and reduce the occurrence of relapses are therefore required.

Factors contributing to relapse and disease rebound

Disease relapse without maintenance therapy is very common in psoriasis and should be expected.[16] In a systematic review and network meta-analyses conducted to evaluate the available topical therapies for the treatment of psoriasis, the percentage of patients relapsing following treatment discontinuation ranged from 20–80% in the short term (4–8 weeks) and was as high as 88% after 6 months.[19] In the current reactive management approach to psoriasis, treatment is often discontinued following successful skin clearance[5]; however, relapses usually occur around 4–8 weeks after treatment discontinuation (Table 1).[13,19]

For a minority of patients, treatment discontinuation can result in worsened disease beyond the severity of their psoriasis at baseline, known as rebound; this is particularly evident if corticosteroid treatment is ended abruptly.[20,21] Studies show that

Table 1 Topical therapies in psoriasis[11]

Therapy	Formulation	Patient acceptance	Efficacy	Adverse events	Duration of remission
Emollients	Multiple OTC lotions, cream, ointments, bath oils	Excellent	Typically does not result in clearance as a monotherapy; used in combination with other therapies	None reported	Not applicable
Salicylic acid	Compounded by pharmacist in concentrations of 2–10% in white petrolatum or other base; OTC scalp solutions, shampoos	Excellent	Typically does not result in clearance as a monotherapy; used in combination with corticosteroids	Risk of salicylate toxicity with application to >20% body surface area	
Corticosteroids	Multiple gels, lotions, creams, ointments, solutions, scalp foams grouped by relative strength (classes 1–7)	Excellent	Thinning of plaques, decreased symptoms in first 2 weeks of treatment, with improvement in subsequent weeks	Local: striae, atrophy, hypopigmentation, telangiectasias, folliculitis, hirsutism Systemic: risk of suppression of HPA axis with excessive and prolonged use	
Tar	Crude coal tar, liquor, carbonis detergens, tar shampoo	Poor†	Thinning of plaques, decreased symptoms within 2–4 weeks	Irritation, folliculitis, photosensitivity	Prolonged, particularly in combination with ultraviolet B light
Anthralin	Commercial formulations, compounded formulations	Poor‡	Thinning of plaques, decreased symptoms within 2–4 weeks	Extremely irritating, must avoid contact to surrounding skin	Prolonged (3–6 months)
Vitamin D analogues	Calcipotriene ointment, cream, scalp solution, gel, foam	Good§	As effective as class 2 corticosteroids; decreased symptoms within 6–8 weeks	Irritation, risk of hypercalciuria and hypercalcemia with >100 g in a week	Mean of 43.3 days
Retinoids	Tazarotene 0.05%, 0.1% gel or cream	Good¶	As effective as class 2 corticosteroids; improvement noted in first 2 weeks of therapy	Irritation, must be used with caution in women of childbearing age	Prolonged

HPA, hypothalamic–pituitary–adrenal; OTC, over-the-counter.

†Stains clothing and skin, has unpleasant odour and causes irritation. ‡Stains clothing, skin and other objects a purple colour, and causes irritation. §Irritation occurs in 15% to 20% of patients especially in groin and on face. ¶Irritation occurs in 30% of patients.

discontinuation of clobetasol after initial skin clearance leads to rebound.[21–23] This can have a negative impact on patients, such as increasing their risk of poor mental well-being and depression.[24]

Reactive treatment fails to induce long-lasting remission despite enabling patients to achieve short-term skin clearance.[16] During disease relapse, the psoriatic lesions tend to recur at the same sites that were previously treated and cleared.[25] This suggests that even though skin may appear clear, there is still residual disease activity below the surface; critical cells, such as tissue-resident memory T cells, may be left behind in the dermis after treatment is stopped and could initiate disease relapse.[25,26]

Data evaluating the residual molecular scars following treatment with topicals are limited; however, there are learnings from studies conducted in patients with residual disease following treatment with biologics. Histological resolution of psoriatic skin lesions is not accompanied by complete resolution of molecular alterations, as assessed by gene profiling. Resolved lesions have a molecular scar comprising 248 gene products that do not return to baseline after treatment.[25] These transcripts can be grouped into inflammation-associated genes such as IL-17, IL-22 (known to be involved in the pathology of psoriasis) and skin structure-related genes including WNT5A and AQP9.[25] In addition, pathogenic memory T cells persist at sites of clinically resolved psoriatic lesions: IL-17-producing αβ T cell clones with psoriasis-specific antigen receptors remain in clinically resolved psoriatic skin lesions.[26,27] These cells likely represent the disease-initiating pathogenic T cells in patients with psoriasis, which could be responsible for causing relapse.[26,27] Although the role of innate cells has not been studied extensively, Langerhans cells isolated from resolved psoriatic lesions can produce IL-23 after stimulation, which makes them another potential activator of resident memory T cells.[28] Collectively, these findings indicate that although the epidermal reaction in psoriasis is fully resolved to the naked eye, the underlying inflammation, as defined by expression of key cytokines and chemokines, is not completely

resolved in all psoriatic lesions and can be stimulated to initiate relapse (Fig. 1).[29]

As well as residual disease reigniting, external triggers can also prompt a disease relapse; these include itch, skin aggression,[30] infections,[31] alcohol and tobacco,[32,33] stress[33] and certain therapeutics (lithium, beta-blockers, antimalarials, angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs).[34] Hormonal changes may also contribute.[35] Regardless of the trigger, relapsing disease can have detrimental effects on patient QoL.

QoL in patients with psoriasis

Patients' lives are severely negatively impacted by psoriasis with the disease affecting their physical, mental and social well-being. Patients with psoriasis often experience difficulties such as maladaptive coping responses, problems with body image, self-esteem and self-concept,[24] and severe itching.[36] Psoriasis is also associated with limitations in patients' daily activities and sexual functioning.[37,38] Patients with psoriasis suffer comparable disability as other patients with chronic illnesses, such as cardiovascular diseases and cancer, as identified by Møller *et al*.[39] who compared the health-related QoL of patients with psoriasis and patients with other major chronic health conditions. As such, depression and suicidal ideation are known to be relatively common in patients with psoriasis.[1,24]

Historically, studies have utilised QoL measures to assess the impact of psoriasis on patients' lives including Dermatology Life

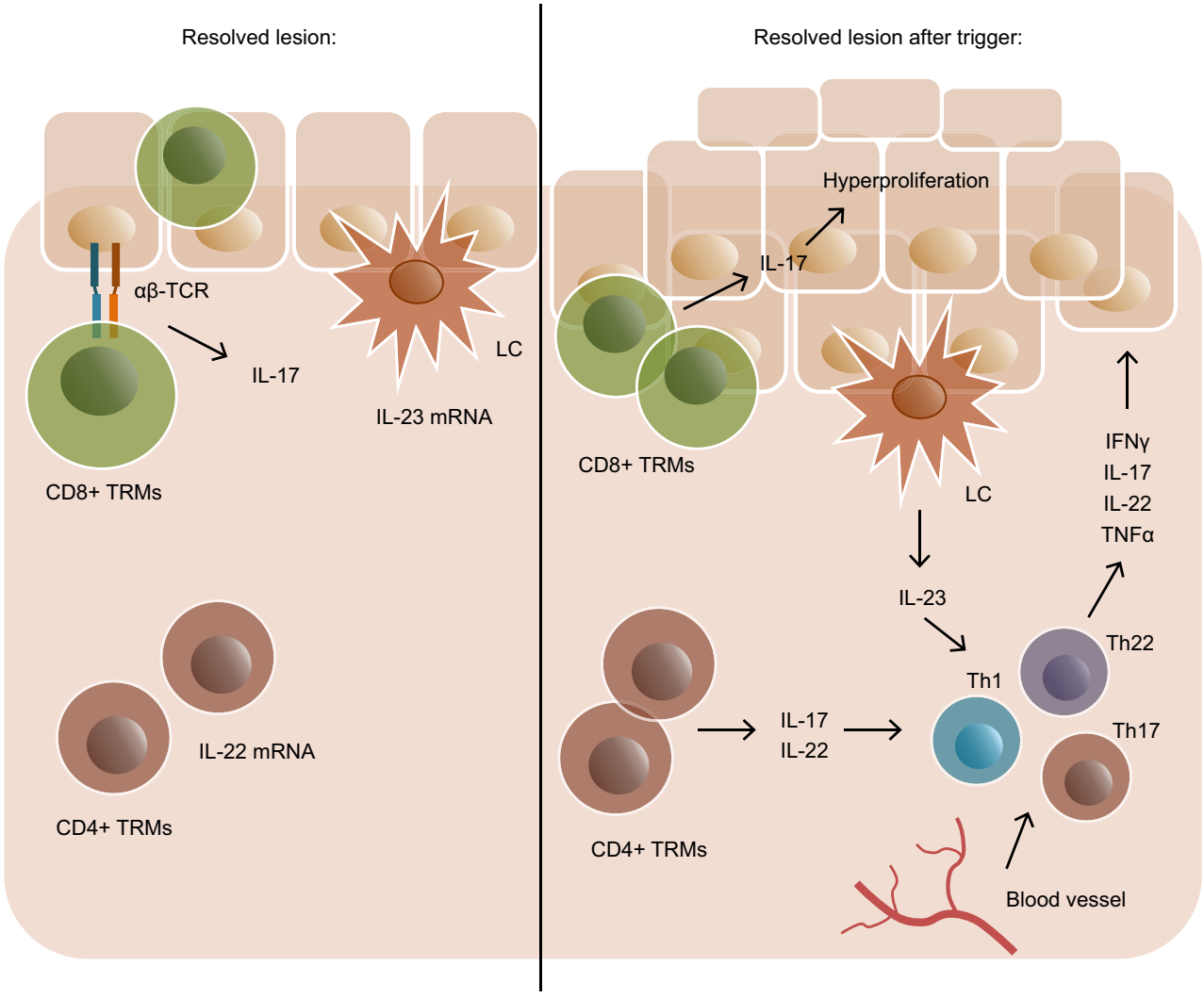

Figure 1 Schematic presenting the mechanism of disease relapse following successful skin clearance.[29] CD, cluster of differentiation; IFN, interferon; IL, interleukin; LC, Langerhans cells; TCR, T cell receptor; Th, T helper; TNF, tumour necrosis factor; TRM, Tissue-resident memory T cell. Originally published in Benezeder *et al*.[29] Reproduced with kind permission from Springer Nature.

Quality Index (DLQI) and EuroQol-5 Dimension (EQ-5D). More recently, the concept of cumulative life course impairment (CLCI) has been introduced, which aims to capture the life-long effects of the disease on patients.[40] The use of CLCI in patients with psoriasis is not yet established; however, reducing the number of flares experienced by patients through a proactive management approach could, in theory, reduce patient vulnerability to disease induced CLCI.[41]

Given that psoriasis is a chronic disease, each relapse can compromise the patient's QoL. One study comparing health-related QoL (HRQoL) outcomes with disease activity in patients ($N = 681$) with psoriasis noted greater disease activity was associated with worse HRQoL; EQ-5D scores were lower with more active disease (remission versus active not flaring vs. active and flaring: 0.93 vs. 0.90 vs. 0.82; $P < 0.05$), while DLQI scores were higher (remission vs. active not flaring vs. active and flaring: 2.0 vs. 5.00 vs. 8.7; $P < 0.05$).[42] Consistent with these findings, another retrospective, cross-sectional study assessing the burden of relapse on HRQoL in patients ($N = 525$) with psoriasis showed that health status level (measured by EQ-5D-3) was reduced in patients who were flaring versus not flaring, with a clinically meaningful difference (>0.074 difference in absolute value; $P = 0.001$). HRQoL measured by DLQI was also significantly reduced ($P = 0.0178$) in patients who were flaring versus not flaring.[43]

Relapses or disease flares are unpredictable and can have detrimental effects on patient QoL; therefore, maintaining long-term remission is paramount for improving both clinical and QoL outcomes for patients with psoriasis.

Long-term proactive management of psoriasis with Cal/BD foam

Long-term proactive management of psoriasis should be considered a mandatory therapeutic strategy, even in the absence of long-term treatment guidelines. This will ensure patients receive appropriate proactive treatment with a view to improving adherence and long-term outcomes.[5] Few studies have assessed the efficacy and safety of long-term use of topicals, and data from maintenance studies longer than 6 months are also lacking. Results from a randomised clinical study assessing Cal/BD foam as a proactive long-term management approach for psoriasis vulgaris to prevent or reduce the occurrence of relapse over 52 weeks (PSO-LONG) have been reported, and have the potential to address some of the challenges associated with long-term management of psoriasis outlined here.[10]

The PSO-LONG study [a Phase III multicentre study comparing the efficacy and safety of Cal/BD foam twice-weekly (proactive treatment; $N = 256$) with vehicle foam twice-weekly (reactive treatment; $N = 265$), 2 or 3 days apart on fixed days, as long-term maintenance therapy (52 weeks) in patients with psoriasis] demonstrated superiority of proactive over reactive management in prolonging time to first relapse, reducing number of relapses and increasing days in remission in adults with psoriasis.[10] This study included an initial open-label phase where 650 patients were instructed to apply Cal/BD foam once -daily to psoriatic lesions on the trunk and/or limbs for 4 weeks. Of these patients, 521 achieved treatment success [physician's global assessment (PGA) score 'clear'/'almost clear' (PGA <2) with ≥2-grade improvement from baseline], at 4 weeks, and were randomised 1 : 1 into the long-term maintenance phase.[10] During this phase, assessment for potential relapse occurred at clinic visits (every 4 weeks) and unscheduled visits as initiated by the patient. Upon relapse, patients from both treatment groups received rescue treatment with Cal/BD foam, applied to lesions once-daily for 4 weeks. If PGA score 'clear'/'almost clear' was regained after 4 weeks' rescue treatment, maintenance treatment (twice-weekly Cal/BD foam) was resumed; if not, patients were withdrawn from the trial.[10]

Sustained remission is not achievable with the current treatment approaches and relapse is inevitable.[16] Providing a proactive, intermittent treatment to maintain response following initial treatment success may be a suitable option to improve patient outcomes. This approach can prolong disease relapse in comparison with reactive treatment. In PSO-LONG, the estimated median time to first relapse from randomisation was prolonged by 26 days for patients in the proactive arm compared with the reactive arm (56 days vs. 30 days, respectively) and the risk of experiencing first relapse was reduced by 43% for proactive versus reactive treatment [hazard ratio, 0.57; 95% confidence interval (CI), 0.47 to 0.69; $P < 0.001$; Fig. 2]. The proportion of days in remission was significantly higher for patients in the proactive versus reactive arm; estimated treatment difference 11% (95% CI, 8 to 14%; $P < 0.001$), corresponding to an additional 41 days in remission over 1 year (Fig. 2).[10]

Treatment adherence is a limiting factor in improving outcomes for patients with psoriasis with long-term topical treatment. A link between treatment dissatisfaction and adherence has been observed resulting from patients being unhappy with the time it takes for treatment to make a notable difference to their psoriasis, leading to early termination or non-compliance with the therapeutic regimen.[4] Thus, a fast-acting treatment could improve patient satisfaction and ultimately outcomes. Data from the PSO-LONG open-label lead-in phase have shown that patients are able to achieve a PGA 'clear' or 'almost clear' within 4 weeks of commencing treatment.[10]

Safety is a concern with long-term topical management of psoriasis, particularly corticosteroids. The safety data from PSO-LONG demonstrate that, overall, Cal/BD foam was well tolerated throughout the study.[10] The rate of serious adverse events (AEs) and treatment-related AEs per 100 patient-years was low and similar between both the proactive and reactive treatment groups: 8.3 proactive and 7.9 reactive and 2.8 proactive and 4.5 reactive, respectively. The rate of severe AEs per 100 patient-years was 4.5 in the proactive group and 8.5 in the reactive group.[13] No new safety concerns were identified over 52 weeks

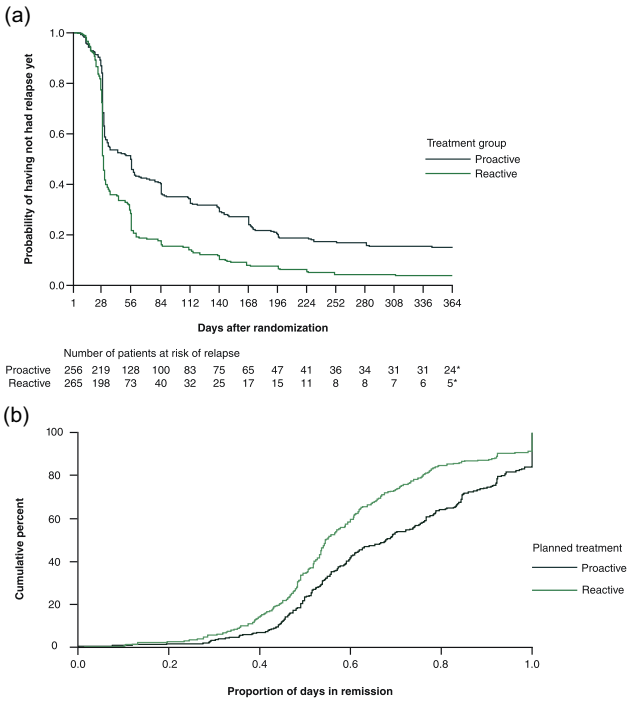

Figure 2 (a) Time to first relapse during the maintenance phase with proactive management or reactive management; (b) cumulative proportion of days spent in remission during the maintenance phase with proactive management or reactive management. Data from PSO-LONG.[10] Note: patients who did not achieve physician's global assessment <2 after 4 weeks of once-daily rescue treatment following relapse were withdrawn from the trial but are included within this Kaplan–Meier curve. *30 patients in the proactive group vs. 6 patients in the reactive group finished the trial without experiencing first relapse but had their final visit prior to Day 364. Originally published in Lebwohl *et al*.[10] Reproduced with kind permission from Elsevier.

and the safety profile was consistent with that observed over the short-term.[10] This safety profile makes Cal/BD foam an attractive option for a long-term proactive management treatment for psoriasis.

Conclusion

The current reactive or treat until skin clearance approach to topical psoriasis treatment is suboptimal at maintaining long-term remission given the fact that following initial skin clearance, residual disease remains, which can trigger relapses within weeks of treatment discontinuation. Strategies to delay relapse or reduce its occurrence should be implemented to manage disease and improve patient QoL. A proactive approach to long-term management of psoriasis vulgaris with topicals, aimed at maintaining disease remission, may be a strategy that could improve clinical and QoL outcomes for patients. More studies are required to fully support a proactive management approach and guide long-term management strategies with topicals; however, results from the PSO-LONG study are very encouraging.

What does this mean for clinical practice?

- Current strategy for long-term reactive management of psoriasis flares with topical treatment is suboptimal and relapse occurs frequently.
- Relapse has a significant impact on patient QoL. Strategies to reduce the occurrence of relapse need to be implemented.
- In the PSO-LONG study, proactive management with Cal/BD foam twice weekly increased time to first relapse, reduced number of relapses and increased days in remission versus reactive management in adults with psoriasis.
- Coupled with the well-characterised safety profile, Cal/BD foam should be considered when prescribing a topical treatment for the long-term proactive management of psoriasis in daily practice.

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